Endokrynologia Polska
10.5603/EP.2017.0022
Tom/Volume 68; Numer/Number 3/2017
ISSN 0423–104X

Models of cognitive functions with respect to selected parameters of functional state of thyroid gland in post-menopausal women

Modele funkcji poznawczych względem wybranych parametrów stanu funkcjonalnego tarczycy u kobiet po menopauzie

Mariusz Gujski[1], Jarosław Pinkas[2], Mariusz Witczak[3], Alfred Owoc[4], Iwona Bojar[5], Dorota Raczkiewicz[6]

[1]*Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Poland*
[2]*School of Public Health, Centre of Postgraduate Medical Education, Warsaw, Poland*
[3]*College of Public Health, Zielona Góra, Poland*
[4]*Centre for Public Health and Health Promotion, Institute of Rural Health in Lublin, Poland*
[5]*Department for Women's Health, Institute of Rural Health in Lublin, Poland*
[6]*Institute of Statistics and Demography, Warsaw School of Economics, Warsaw, Poland*

Abstract

Introduction: The objective of the study was the development of models of cognitive functions in a group of post-menopausal women, according to the concentration of the selected laboratory parameters evaluating the functional state of the thyroid gland.

Material and methods: The study was conducted during 2012–2014, and covered women aged 50–65 years, minimum two years after the last menstruation, without chronic diseases, cancerous diseases, mental disorders, addiction to drugs or alcohol, and who did not use hormone replacement therapy. At the stage of qualification, a brief MoCA test was performed; 383 women were qualified for the study. Blood was collected for the determination of such parameters as: TSH, TT4, fT4, anti-TPO, anti-Tg, and AB-TSHR. Assessment of cognitive functions was performed using the diagnostic instrument Central Nervous System — Vital Signs (CNS-VS) (Polish version). The results were statistically analysed.

Results: The mean age of the women in the study was 56.4 ± 3.4; the mean TSH was 1.91 ± 1.35 mU/L, fT4 14.76 ± 2.34 pmol/L, and TT4 99.12 ± 16.98 nmol/L. Mean values were: 64.74 IU/L for anti-TPO, 100.69 IU/L for anti-Tg, and 1.40 IU/L for AB-TSHR. The examined women obtained the neurocognitive index (NCI) on the level of 84.4 scores, on average. The lowest results were obtained in tests assessing cognitive flexibility (mean 78.64 scores), processing speed (mean 79.25 scores), and executive functions (mean 79.75 scores). In the tests evaluating complex attention, the mean values were 82.24 scores, psychomotor speed — mean 83.42 scores, and reaction time — mean 86.87 scores. The women examined obtained the best results in tests assessing memory (mean 90.15 scores), including verbal (mean 91.22 scores), and visual (mean 93.37 scores).

The NCI and cognitive function models were assessed from the aspect of thyroid gland examinations in post-menopausal women. Based on the analyses performed, the following conclusions were drawn:

1. The developed models of cognitive functions indicate a considerable effect of TSH, fT4, AB-TSHR, and anti-TPO, as well as TT4 and anti-Tg, on the level of cognitive functions after menopause in the group examined.
2. The conducted study suggests the need for examination of the functional state of the thyroid gland in post-menopausal women who show cognitive function disorders. **(Endokrynol Pol 2017; 68 (3): 290–298)**

Key words: *cognitive functions; thyroid; menopause*

Streszczenie

Wstęp: Celem pracy było opracowanie modeli funkcji poznawczych w grupie kobiet po menopauzie w zależności od stężenia wybranych parametrów laboratoryjnych oceniających stan funkcjonalny tarczycy.

Materiał i metody: Badanie przeprowadzono w latach 2012–2014. Zbadano kobiety w wieku 50–65 lat; minimum 2 lata od ostatniej miesiączki, bez chorób przewlekłych, chorób nowotworowych, chorób psychicznych, uzależnień od leków i alkoholu oraz nieprzyjmujące hormonalnej terapii zastępczej. Na etapie kwalifikacji przeprowadzono krótki test MoCA. Do badania zakwalifikowano 383 kobiety. Badanym pobrano krew do oznaczeń takich parametrów, jak: TSH, TT4, fT4, anty-TPO, anty-Tg, AB-TSHR. Ocenę funkcji poznawczych przeprowadzono na podstawie aparatury diagnostycznej funkcji poznawczych CNS-VS (wersja polska). Wyniki poddano analizie statystycznej.

Wyniki: Średnia wieku badanych kobiet wynosiła 56,4 ± 3,4 roku. Badane miały TSH średnio 1,91 ± 1,35 mU/l, fT4 14,76 ± 2,34 pmol/l i TT4 99,12 ± 16,98 nmol/l. Średnie wartości wynosiły 64,74 IU/l dla anty-TPO, 100,69 IU/l dla anty-Tg i 1,40 IU/l dla AB-TSHR. Badane kobiety uzyskały indeks neurokognitywny (NCI) średnio na poziomie 84,4 pkt. Najniższe wyniki uzyskały w testach oceniających plastyczność poznawczą (średnio 78,64 pkt.), szybkość przetwarzania (średnio 79,25 pkt.) i funkcje wykonawcze (średnio 79,75 pkt.). Wyniki w testach oceniających skupianie uwagi wynosiły średnio 82,24 pkt., szybkość psychomotoryczną — średnio 83,42 pkt. oraz czas reakcji — średnio 86,87 pkt. Najlepsze wyniki osiągnęły badane kobiety w testach oceniających pamięć (średnio 90,15 pkt.), w tym werbalną (średnio 91,22 pkt.) i wzrokową (średnio 93,37 pkt.).

Iwona Bojar M.D., Department for Women's Health, Institute of Rural Health in Lublin, Jaczewskiego St. 2, 20–090 Lublin, Poland, phone: +48 81 718 44 10, faks: +48 81 747 86 46, e-mail: iwonabojar75@gmail.com

Wnioski: Oszacowano modele NCI i funkcji poznawczych względem badań tarczycowych u kobiet po menopauzie. Na podstawie przeprowadzonych analiz wyciągnięto wnioski:
1. Opracowane modele funkcji poznawczych wskazują na znaczny wpływ TSH, FT4, AB-TSHR i anty-TPO, jak również TT4 i anty-Tg na poziom funkcji poznawczych po menopauzie w badanej grupie.
2. Przeprowadzone badanie sugeruje potrzebę badania stanu funkcjonalnego tarczycy u kobiet po menopauzie wykazujących zaburzenia funkcji poznawczych.

(Endokrynol Pol 2017; 68 (3): 290–298)

Słowa kluczowe: *funkcje poznawcze; tarczyca; menopauza*

Introduction

In recent years, civilisation progress and tremendous advances in medicine have resulted in a considerable prolongation of the human life span. In developed countries, the mean life span of women exceeds 80 years [1, 2]. Therefore, it is very important to recognise the mechanisms regulating the processes of ageing of the human body, which concern many systems and organs, including the endocrine system. Menopause in women is associated with the cessation of the reproductive ovarian function, and thus the loss of fertility and many somatic and mental disorders [3–6]. In Poland, the mean age at menopause is 51.25 years [7]. Despite the prolongation of life span, the mean age at menopause has not changed for many years. According to the data quoted, a woman lives one third of her lifetime after menopause. Thus, this is not a period of decline, but a subsequent stage in a woman's life.

Hormonal changes taking place in woman's body after menopause are responsible for the development of many disorders and complaints. During this period there develop in women psychological, somatic, and vasomotor symptoms of the menopausal syndrome; incontinence is more frequent, there occur changes in the connective tissue, as well as in the bone tissue, leading to the development of postmenopausal osteopaenia and osteoporosis. All these changes decrease the quality of life of women during this period [8, 9]. The fact of the deterioration of cognitive functions with age is well known [10]. In post-menopausal women, a decline was observed in the efficacy of cognitive functions, which fall below the average for the general population. It was confirmed that women obtained the worst results with respect to the speed of processing, cognitive plasticity, and executive functions, whereas the best results were with respect to verbal memory and visual memory [11]. The theory of these changes that is most frequently considered is a rapid decline in sex hormones after menopause, and in consequence, the deterioration of cognitive functions. This theory has been confirmed by many studies, which showed the neuroprotective role of oestrogens and androgens on the nerve cells [12–14]. Nevertheless, investigations of the effect of oestrogen supplementation on cognitive functions after menopause did not bring about an unequivocal confirmation of this theory [15–17].

Dysfunctions of the thyroid gland commonly occur in the general population, especially among women. The effect of thyroid hormones on metabolism, including the metabolism of the brain, has been known for years; however, the effect of the thyroid hormones on the brain has not been fully explained. It was found that thyroid hormones exert an effect on brain metabolism, modulate gene expression, and affect the transmission of signals between cells, among others, by the synthesis of enzymes necessary for the production of neurotransmitters [18]. The effect of thyroid hormones in known on the neurotransmitter systems: noradrenergic, serotonergic, and GABA-ergic. The effect of thyroid hormones on the brain in adults probably takes place by the regulation of activity and synthesis of G proteins. The deficiency of thyroid hormones impairs the transmission of signals via adenylyl cyclase and phosphoinositide [19]. According to the most recent hypothesis, thyroid hormones regulate brain functions mainly through the effect on the catecholaminergic system [20].

The scope of problems concerning cognitive function disorders in thyroid function disorders has been considerably more poorly recognised and at present is the subject of many studies. Studies concerning the relationship between menopause and thyroid function are scarce and do not explain whether menopause has an effect on the thyroid gland, irrespective of ageing, or whether the changes taking place in the thyroid gland with age affect the course of natural menopause. The major changes in the area of physiology and function of the thyroid gland related with the ageing process are: decrease in the uptake of iodine in the thyroid gland, decrease in the synthesis of free thyroxine and triiodothyronine, an increase in free thyroxine catabolism, and an increase in reverse triiodothyronine. Most often, the TSH level remains normal; however, with time it shows a tendency towards the upper limit. The researchers report that menopause may modify clinical expression of some thyroid gland diseases, especially autoimmune [21].

The objective of the study was development of the models of cognitive functions in a group of post-

menopausal women, according to the concentration of the selected laboratory parameters evaluating the functional state of the thyroid gland.

Material and methods

The study group were women from the south-eastern areas of Poland. The study was conducted during 2012–2014. The criteria for enrolment into the study were: age 50–65 years; education at least completed primary, and a minimum of two years after the last period. The criteria of exclusion from the study were as follows: chronic diseases within the last five years before recruitment, including a diagnosed thyroid gland disease; an active cancerous disease within the last five years before recruitment; mental disease in medical history; addiction to drugs and alcohol; and a disease unit with dementia symptoms diagnosed.

At the stage of qualification to the study, a brief MoCA test was performed in order to include into the study the women who do not show the features of dementia. The maximum number of scores in this test is 30, and the result of 26 or more scores is considered as normal. All the examined women who were included into the further stages of the study obtained more than 26 scores in the MoCA test [22].

Blood was collected from the examined women for the determination of such parameters as: thyroid-stimulating hormone, total thyroxine (TT4), free thyroxine (fT4), anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroid peroxidase antibodies (anti-Tg), and TSH receptor antibodies (AB-TSHR). The blood samples were immediately delivered to the laboratory. The determinations were performed in an accredited SYNEVO Laboratory.

Cognitive functions were assessed by means of the diagnostic instrument for the assessment of cognitive functions — Central Nervous System — Vital Signs *(*CNS-VS*)* (Polish version), using the CNS Vital Signs, 1829 East Franklin Street, Bldg 500, Chapel Hill, NC 27514, 919-933-0932 software. The instrument, in the form of a battery of computer tests, was subjected to the full validation procedure. The validation procedure on a computer was performed in Polish [23]. The tests were performed under the supervision of a psychologist.

The presented cognitive functions were evaluated as the following domains: memory, verbal memory, visual memory, processing speed, executive functions, psychomotor speed, reaction time, complex attention, and cognitive flexibility.

Mean standardised results obtained from the tests were used for the calculations. The clinical report from the CNS Vital Signs test classifies the examined women into five groups, according to the Neurocognitive Index (NCI), and nine cognitive functions. Standardised results are calculated in a way to classify the examined women into intervals described as: 5 — above average (> 109), 4 — average (90–109), 3 — below average (80–89), 2 — low (70–79), 1 — very low (< 70).

The report from the CNS VS test provides the value of the Neurocognitive Index, which is computer calculated in an integrated way, based on five domains: memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility.

The collected data were statistically analysed using the statistical software package STATISTICA. Tables presented the minimum and maximum values, arithmetic mean (*M)*, and standard deviations (*SD*), absolute number (*n*), and relative number (ratio between the number of units of a given feature variant to the number of the sample expressed in %).

Ten NCI regression models and cognitive functions were assessed with respect to the characteristics of the thyroid gland in the women examined. The explained variable was first the Neurocognitive Index and then the subsequent cognitive functions (standard scores). The explanatory variables were characteristic of the thyroid gland. The selection of the explanatory variables to the models were performed by the method of step-wise regression forward until the moment when all the explanatory variables in the models were statistically significant. As a measure of the quality of regression models, the coefficient of multiple correlation was adopted, and the coefficient of determination, which is its square. In statistical tests the level of significance was set at $\alpha = 0.05$.

The study covered 383 postmenopausal women, aged 50–65 years; mean age 56.4 ± 3.4 years.

The study obtained approval from the Bioethics Committee at the Institute of Rural Health in Lublin.

Results

The functional state of the thyroid gland in the examined women was assessed based on the concentration of: TSH, fT4, TT4, and anti-thyroid antibodies (anti-TPO, anti-Tg, and AB-TSHR). The women in the study had a mean TSH level of 1.91 ± 1.35 mU/L, fT4 mean 14.76 ± 2.34 pmol/L, and TT4 mean 99.12 ± 16.98 nmol/L. The mean concentrations of anti-thyroid antibodies were 64.74 IU/L for anti-TPO, 100.69 IU/L for anti-Tg, and 1.40 IU/L for AB-TSHR (Table I).

The women in the study obtained the Neurocognitive Index on the level of 84.4 scores, on average, showing a general assessment of cognitive functions on a level lower than the general average. The examined women obtained the worst results in tests evaluating cognitive flexibility (mean 78.64 scores), processing speed (mean 79.25 scores), and executive functions

Table I. *Selected parameters of the functional status of the thyroid gland in the examined women*
Tabela I. *Wybrane parametry stanu funkcjonalnego tarczycy u badanych kobiet*

Characteristics of thyroid gland	Unit	Min–Max	M ± SD	Below normal	Normal	Above normal
				%	%	%
TSH	mU/L	0.27–7.36	1.91 ± 1.35	0.00	91.91	8.09
fT4	pmol/L	9.32–22.16	14.76 ± 2.34	11.23	88.25	0.52
TT4	nmol/L	62.99–146.70	99.12 ± 16.98	1.57	98.43	0.00
Anti-TPO	IU/L	5.00–600.00	64.74 ± 125.04	0.00	75.46	24.54
Anti-Tg	IU/L	8.00–800.20	100.69 ± 161.56	0.00	76.24	23.76
AB-TSHR	IU/L	0.31–3.80	1.40 ± 0.56	0.00	60.31	39.69

Table II. *Cognitive functions (standardised results) of the examined women*
Tabela II. *Funkcje poznawcze (wyniki standaryzowane) badanych kobiet*

Cognitive functions	Min–Max	M ± SD	Evaluations				
			Very low	Low	Low average	Average	Above
	Standard scores		%	%	%	%	%
NCI	29–115	84.41 ± 16.24	16.97	20.10	15.14	46.48	1.31
Memory	44–128	90.15 ± 15.65	8.36	18.02	24.28	32.38	16.97
Verbal memory	42–125	91.22 ± 17.75	9.92	14.62	16.71	38.64	20.10
Visual memory	47–125	93.37 ± 15.03	5.74	10.44	25.07	46.74	12.01
Processing speed	26–117	79.25 ± 14.35	22.19	26.37	24.02	25.85	1.57
Executive functions	18–124	79.75 ± 25.08	29.50	11.75	16.45	32.11	10.18
Psychomotor speed	22–116	83.42 ± 18.07	18.28	14.36	24.28	37.60	5.48
Reaction time	36–121	86.87 ± 16.72	11.49	16.97	26.37	40.47	4.70
Complex attention	6–121	82.24 ± 28.64	24.02	12.53	12.79	37.08	13.58
Cognitive flexibility	18–125	78.64 ± 26.08	26.37	15.40	16.71	31.85	9.66

(mean 79.75 scores), which indicated low evaluations of these cognitive functions. Slightly better results were obtained in tests assessing complex attention (mean 82.24 scores) and psychomotor speed (mean 83.42 scores), and even better with respect to the reaction time (mean 86.87 scores), showing the evaluations of these cognitive functions below average. The examined women obtained the best results in tests assessing memory (mean 90.15 scores), including verbal memory (mean 91.22 scores) and visual memory (mean 93.37 scores), which indicated the average evaluations of these cognitive functions (Table II).

Table III shows the result of assessments of the NCI models and cognitive functions (scores) with respect to the parameter examined. The coefficients of multiple correlation, and consequently the coefficients of determination for all models, are statistically significant ($p \leq 0.05$).

Figure 1 illustrates the significant effect of the examined thyroid gland parameters on NCI and cognitive functions of postmenopausal women.

For the models of the Neurocognitive Index, executive functions, and cognitive flexibility, a similar set of thyroid gland parameters was obtained (TSH, TT4, and AB-TSHR), the effect of which on those functions was significantly negative.

The Neurocognitive Index was lower by 0.14 scores, on average, if the TSH level was higher by 0.1 mU/L; 0.09 scores if the concentration of TT4 was higher by nmol/L; and 0.42 scores if the level of AB-TSHR was higher by 0.1 IU/L.

The results for cognitive functions were lower, on average, by 0.30 scores if the TSH level was higher by 0.1 mU/L; 0.18 scores if the concentration of TT4 was higher buy 1 nmol/L; and 0.66 scores if the level of AB-TSHR was higher by 0.1 IU/L.

The results concerning cognitive flexibility were lower, on average, by 0.28 scores if the level of TSH was higher by 0.1 mU/L; 0.18 scores if the concentration of TT4 was higher by 1 nmol/L; and 0.67 scores of the level of AB-TSHR was higher by 0.1 IU/L.

Table III. *Assessment of cognitive function models with respect to the functional state of the thyroid gland in the examined women*

Tabela III. *Oszacowania modeli funkcji poznawczych względem stanu funkcjonalnego tarczycy u badanych kobiet*

Cognitive function	Parameter	Assessment	Standard deviation	t	p	R	F	p
NCI	Intercept	101.92	5.29	19.284	< 0.001	0.216	6.212	< 0.001
	AB-TSHR [IU/L]	–4.21	1.48	–2.849	0.005			
	TSH [mU/L]	–1.39	0.61	–2.284	0.023			
	TT4 [nmol/L]	–0.09	0.05	–1.815	0.070			
Memory	Intercept	103.20	4.70	21.974	< 0.001	0.194	7.428	< 0.001
	Anti TPO [IU/L]	–0.02	0.01	–2.950	0.003			
	TT4 [nmol/L]	–0.12	0.05	–2.577	0.010			
Verbal memory	Intercept	106.01	5.29	20.021	< 0.001	0.222	9.843	< 0.001
	TT4 [nmol/L]	–0.13	0.05	–2.520	0.012			
	Anti TPO [IU/L]	–0.03	0.01	–3.733	< 0.001			
Executive functions	Intercept	112.08	8.09	13.858	< 0.001	0.253	8.665	< 0.001
	AB-TSHR [IU/L]	–6.57	2.26	–2.907	0.004			
	TSH [mU/L]	–2.98	0.93	–3.188	0.002			
	TT4 [nmol/L]	–0.18	0.08	–2.309	0.021			
Psychomotor speed	Intercept	71.04	5.93	11.970	< 0.001	0.162	5.100	0.007
	fT4 [pmol/L]	0.90	0.39	2.299	0.022			
	Anti TPO [IU/L]	–0.01	0.01	–1.990	0.047			
Reaction time	Intercept	85.59	1.00	85.510	0.000	0.123	5.862	0.016
	Anti TG [IU/L]	0.01	0.01	2.421	0.016			
Complex attention	Intercept	87.72	2.51	34.910	< 0.001	0.136	7.152	0.008
	TSH [mU/L]	–2.87	1.07	–2.674	0.008			
Cognitive flexibility	Intercept	110.92	8.44	13.139	< 0.001	0.240	7.710	< 0.001
	AB-TSHR [IU/L]	–6.68	2.36	–2.832	0.005			
	TSH [mU/L]	–2.77	0.98	–2.835	0.005			
	TT4 [nmol/L]	–0.18	0.08	–2.238	0.026			

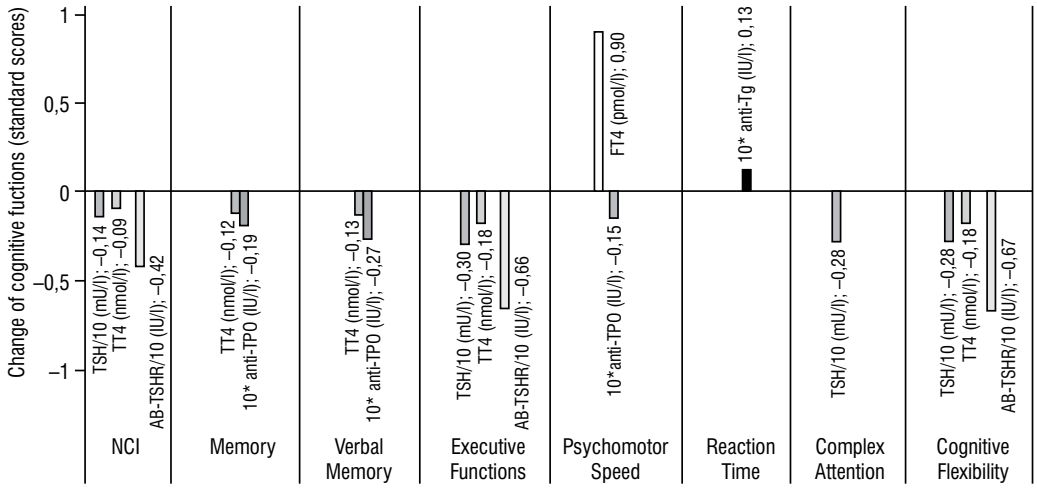

Figure 1. *Changes in the results for cognitive functions (scores) conditioned by an increase in thyroid gland characteristics in the examined women*

Rycina 1. *Zmiany wyników funkcji poznawczych (pkt.) warunkowane wzrostem charakterystyk tarczycy u badanych kobiet*

A similar set of thyroid gland characteristics was obtained for the models of memory and verbal memory (TT4 and anti-TPO), the effect of which on these functions was significantly negative.

The results for memory were lower, on average, by 0.12 scores if the concentration of TT4 was higher by 1 nmol/L; and 0.19 scores if the concentration of anti-TPO was higher by 10 IU/L. The results for verbal memory were lower on average by 0.13 scores if the concentration of TT4 was higher by 1 nmol/L; and 0.27 scores if the concentration of anti-TPO was higher by 10 IU/L.

For the models of psychomotor speed, reaction time, and complex attention, various sets of thyroid gland characteristics were obtained, which exerted a significant effect on these functions.

The results of psychomotor speed were higher, on average, by 0.90 scores if the concentration of fT4 was higher by 1 pmol/L; and lower, on average, by 0.15 scores when the concentration of anti-TPO was higher by 10 IU/L.

The results concerning the reaction time were higher, on average, by 0.13 scores if the concentration of anti-Tg was higher by 10 IU/L.

The results for complex attention were lower, on average, by 0.28 scores if the TSH level was higher by 0.1 mU/L.

Discussion

Observations encouraging the search for causes of cognitive disorders in the group of women after menopause result from the fact that Alzheimer's disease more often afflicts females than males [24–26]. Usually, an acceleration of its development is observed in postmenopausal women.

Results of the CNS VS tests in our own studies of postmenopausal women allowed characterisation of NCI and cognitive functions of the women in the study. They obtained worse results with respect to NCI, memory, cognitive flexibility, executive functions, reaction time, psychomotor speed, and processing speed. In these domains, more than a half of the women obtained evaluations below average, poor, or very poor. Definitely the greatest disorders occurred with respect to the processing speed, where more than 70% of the women obtained results below average. The highest percentage of very poor evaluations was obtained by the women in the study with respect to executive functions, cognitive flexibility, complex attention, and processing speed. The least disorders were found in the tests assessing verbal memory and visual memory. In the WHIMS study conducted among slightly older women, aged over 65 years, the cognitive deficit in at least one domain was present in 82.1% of the study participants, and in the majority of them (74.3%) deficits occurred in many cognitive domains [27]. The results obtained in our own study and the WHIMS reports confirm that postmenopausal women may be a group burdened with an especially high risk of the development of dementia. Researchers from California University confirmed that the processing speed of information declines in the early and late perimenopausal period; however, according to these researchers verbal memory also deteriorates [28].

Despite the fact that the thyroid function plays its role in cognition, the relationship between the state of the thyroid gland and neuropsychiatric symptoms still remains unclear in individuals without clinical symptoms of thyroid disorders or laboratory results in euthyreosis. In our own study, an attempt was undertaken to investigate the relationship between various parameters of thyroid gland functioning and cognitive functions in postmenopausal women without clinical symptoms of thyroid gland diseases. The considerations covered not only TSH and thyroid hormones (TT4 and fT4), but also anti-thyroid antibodies (anti-TPO, anti-Tg, and AB-TSHR). In the results of the study, the high percentage of women with elevated AB-TSHR values and lack of other indicators of thyroid function disorders deserves attention. Possibly, the values slightly above the normal value (maximum concentration 3.8 IU/L) do not exert any significant effect on the thyroid function, and this is a transient state. The limitation of the presented study is the lack of follow-up examinations after the specified period of time.

It was found that in the developed models the results for NCI, executive functions, and cognitive flexibility decreased if the concentration of TSH, TT4, and AB-TSHR increased. The greatest deterioration effect on the above-mentioned functions was exerted by the concentration of AB-TSHR. The results for complex attention in the examined postmenopausal women were lower if the level of TSH was higher. In the model of memory and verbal memory the results were lower if the concentration of TT4 and anti-TPO increased. An increase in the concentration of anti-TPO exerted the greatest effect on the deterioration of memory. In the model for psychomotor speed, the examined women obtained higher results with an increase in fT4, and lower results with an increase in anti-TPO. In the reaction time model, the results were higher, together with an increase in anti-Tg.

The studies conducted by Italian researchers among 337 older people without clinical thyroid gland disorders, who were assessed with respect to cognitive functions using the tests: Mini Mental State Examination (MMSE), Prose Memory Test (PMT), and Matrix Test (MT), a nega-

tive correlation was found between TSH and results for MMSE, PMT, and MT, which is in accordance with the results of our own study. However, no relationship was observed between the levels of fT4 and the results of the tests: MMSE, PMT, and MT [29]. Nevertheless, these results cannot be directly referred to our own studies because the mean age of the population examined was 74.3, i.e. 20 years more than in our own material.

Based on the data obtained in the study Healthy Aging in Neighbourhoods of Diversity Across the Life Span (HANDLS) study cognitive functions were assessed using 13 cognitive functions tests, which covered, among others, such examined domains as: learning, memory, verbal memory, visual memory, psychomotor speed, executive functions. It was confirmed that an elevated concentration of fT4 correlated with better results in the tests of spatial perception in the whole group examined, as well as among females and Afro-Americans. A higher concentration of fT4 positively correlated with perception abilities and memory in the group of women and Afro-Americans. Higher concentrations of TT4 correlated with better results with respect to psychomotor speed, whereas higher levels of hormones fT4 and TT4 correlated with better results in verbal tests in the group of males. The levels of TSH below the reference values correlated with better psychomotor speed and complex attention tests [30]. The results of this study confirm the results obtained in our own study in a group of women where the TSH values negatively correlated with the results obtained for executive functions, complex attention, and cognitive flexibility, whereas the level of fT4 positively correlated with the results for psychomotor speed. The relationship between TT4 and lower results of cognitive functions may result from the effect of thyroid hormone binding proteins. This requires further explanation in scientific studies.

Similar results with respect to TSH were obtained by Hogervorst et al. in a study that covered a group of 1047 people; mean age 64 years. During two years of observation, he discovered that high levels of TSH positively correlated with worse results in the MMSE test. This researcher obtained different results with respect to fT4, finding that high normal concentrations of fT4 positively correlated with worse results in the MMSE, and deterioration of the test results by at least 4 scores within two years of observation [31]. Choi et al. also noted that a higher concentration of fT4 in individuals with euthyreosis was related with worse results for executive functions [32].

Results similar to own studies were obtained by Gunnarsson et al., where a decrease in memory negatively correlated with the concentrations of TT4 in serum, and positively with the levels of TSH in serum [33]. Also, studies by Boxtel et al. conducted in a group of 120 individuals aged 49–71 years confirm the above-mentioned results. They observed a negative correlation between the level of TSH and memory [34].

Other results were presented by the authors of a meta-analysis of 23 studies, who evaluated the relationship between low levels of TSH and cognitive functions. Based on 14 correctly designed and correctly conducted studies, they showed a relationship between sub-clinical hyperthyroidism and cognitive function disorders or dementia [35]. Other researchers also found that in the elderly without dementia, low TSH was related with the deterioration of cognitive functions [36, 37].

Nevertheless, the report from the study of a group of 5154 males and females aged 70–82 years, without an earlier diagnosis of thyroid function disorders, where the cognitive functions were tested using five neuropsychological tests — in the beginning of the study and after subsequent time points during observation lasting for three years — did not report any differences between the result of cognitive tests in sub-clinical hyperthyroidism and hypothyroidism with respect to the results of cognitive tests among study participants with euthyreosis [38]. Similar results were presented by Ojala et al. [39].

In our own study conducted among postmenopausal women, the relationship was also analysed between the level of anti-thyroid antibodies and cognitive function disorders. On the one hand, this is important because, according to literature, at the age of over 60 years the susceptibility to autoimmune diseases is higher [40], including autoimmune thyroid gland diseases, which actually constitute the main cause of hypothyroidism; and on the other hand, menopausal transition may also modify the clinical expression of selected thyroid gland diseases, especially autoimmune [21]. In our own studies of women after menopause but not older than 65 years, a high percentage of anti-thyroid antibodies was also found. Similar data are reported by Resta et al. [41]. They found that older women, irrespective of age, are more often afflicted by thyroid gland disease than males. They also confirmed that the frequency of occurrence of autoimmune thyroid gland diseases is higher among women aged over 60 years, which is shown by a more frequent occurrence of antithyroid antibodies at this age [41]. According to the studies, it cannot be excluded that the autoimmune phenomena taking place in the thyroid gland, irrespective of their effect on the thyroid gland function, may play a direct role in the impairment of the cognitive status observed in the older population with sub-clinical hypothyroidism [42].

In our own study, a significant negative effect of anti-TPO was observed in the results for memory, verbal memory, and psychomotor speed. The concentration of anti-Tg positively correlated with the results for reaction time. In turn, the level of antibodies against TSH receptor was negatively related with the results of NCI, executive functions, and cognitive flexibility.

In a previously quoted study by Grigorova et al., and similar to our own study, the level of anti-thyroid antibodies on cognitive functions was evaluated. It was observed that higher concentrations of anti-thyroglobulin antibodies positively correlated with a larger number of mistakes in the Trial Making Test Part B, in the Word Fluency test, and in the Design Fluency test. The researchers suggest that a higher concentration of TgAB, but within normal values, may exert a negative effect on executive functions, which was not confirmed in our own study [43]. Many other studies confirm the negative effect of high titres of anti-thyroglobulin and anti-thyroid peroxidase antibodies on the results of cognitive functions [44, 45].

Despite the above-presented reports, Regal mentioned that after the correction of data for multiple comparisons in the analysis of variance, no correlations were observed between titres of anti-thyroglobulin and anti-thyroid peroxidase antibodies in the analysed cognitive tests [46].

In the context of the presented study, the study conducted among patients with hyperthyroidism in the course of Graves-Basedow disease is interesting. Important disorders are presented with respect to operative memory and executive functions related with the function of the prefrontal cortex of the brain, compared to healthy individuals [47]. This could be consistent with the results obtained in the presented study, provided that the majority of persons with Graves-Basedow disease had increased titres of AB-TSHR antibodies, because in this study it was found that the concentration of antibodies against TSH receptor negatively correlated with the results of NCI, executive functions, and cognitive flexibility.

Conclusions

The developed models of cognitive functions show a considerable effect of TSH, fT4, AB-TSHR, and anti-TPO, as well as TT4 and anti-Tg, on the level of cognitive functions after menopause in the examined group. This suggests the need for studies on the functional state of the thyroid gland in postmenopausal women showing cognitive functions disorders.

References

1. EUROSTAT Eurostat database Available at: http://epp eurostat.ec.europa eu.
2. Witkowski J (przew.). Rocznik Demograficzny. Główny Urząd Statystyczny, Warszawa 2012; 62: 404,490,518-521.
3. Stachowiak G, Pertyński T, Pertyńska-Marczewska M. Effect of transdermal hormone therapy on platelet haemostasis in menopausal women. Ann Agric Environ Med. 2015; 22(1): 167–171, doi: 10.5604/12321966.1141389, indexed in Pubmed: 25780849.
4. Humeniuk E, Bojar I, Owoc A, et al. Psychosocial conditioning of depressive disorders in post-menopausal women. Ann Agric Environ Med. 2011; 18(2): 441–445, indexed in Pubmed: 22216827.
5. Bojar I, Wojcik-Fatla A, Owoc A, et al. Polymorphisms of apolipoprotein E gene and cognitive functions of postmenopausal women, measured by battery of computer tests — Central Nervous System Vital Signs. Neuro Endocrinol Lett. 2012; 33(4): 385–392, indexed in Pubmed: 22936261.
6. Milewicz A. Fizjologiczne i endokrynologiczne aspekty okresu klimakterium. W: Endokrynologia kliniczna. Milewicz A (red.). Polskie Towarzystwo Endokrynologiczne, Wrocław 2012; T 3: 66–67.
7. Kaczmarek M. Określenie wieku menopauzy naturalnej w populacji polskich kobiet. Przegl Menop. 2007; 2: 77–82.
8. Robak-Chołubek D, Wdowiak A, Makara-Studzińska M, et al. Perception and degree of acceptance of menopause-related changes in various spheres of life by postmenopausal women. Ann Agric Environ Med. 2014; 21(3): 666–669, doi: 10.5604/12321966.1120622, indexed in Pubmed: 25292149.
9. Janiszewska M, Firlej E, Dziedzic M, et al. Health beliefs and sense of one's own efficacy and prophylaxis of osteoporosis in peri- and post-menopausal women. Ann Agric Environ Med. 2016; 23(1): 167–173, doi: 10.5604/12321966.1196875, indexed in Pubmed: 27007538.
10. Bégin ME, Langlois MF, Lorrain D, et al. Thyroid Function and Cognition during Aging. Curr Gerontol Geriatr Res. 2008: 474868, doi: 10.1155/2008/474868, indexed in Pubmed: 19415145.
11. Bojar I, Wierzbińska-Stępniak A, Witczak M, et al. Are cognitive functions in post-menopausal women related with the contents of macro- and micro-components in the diet? Ann Agric Environ Med. 2015; 22(1): 178–184, doi: 10.5604/12321966.1141391, indexed in Pubmed: 25780851.
12. Colzato LS, Pratt J, Hommel B. Estrogen modulates inhibition of return in healthy human females. Neuropsychologia. 2012; 50(1): 98–103, doi: 10.1016/j.neuropsychologia.2011.11.003, indexed in Pubmed: 22093437.
13. Bowers JM, Waddell J, McCarthy MM. A developmental sex difference in hippocampal neurogenesis is mediated by endogenous oestradiol. Biol Sex Differ. 2010; 1(1): 8, doi: 10.1186/2042-6410-1-8, indexed in Pubmed: 21208470.
14. Carroll JC, Rosario ER. The potential use of hormone-based therapeutics for the treatment of Alzheimer's disease. Curr Alzheimer Res. 2012; 9(1): 18–34, indexed in Pubmed: 22329650.
15. Yaffe K, Vittinghoff E, Ensrud KE, et al. Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. Arch Neurol. 2006; 63(7): 945–950, doi: 10.1001/archneur.63.7.945, indexed in Pubmed: 16831962.
16. LaCroix AZ, Chlebowski RT, Manson JE, et al. WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA. 2011; 305(13): 1305–1314, doi: 10.1001/jama.2011.382, indexed in Pubmed: 21467283.
17. Grady D, Yaffe K, Kristof M, et al. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. Am J Med. 2002; 113(7): 543–548, indexed in Pubmed: 12459399.
18. Dąbkowska M, Augustyńska B, Odrowąż-Sypniewska G, et al. Poziom hormonu tyreotropowego a wybrane funkcje poznawcze u chorych na schizofrenię. Postępy Psychiatrii i Neurologii. 2008; 17(1): 29–33.
19. Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. Mol Psychiatry. 2002; 7(2): 140–156, doi: 10.1038/sj.mp.4000963, indexed in Pubmed: 11840307.
20. Derkacz M, Michałojc-Derkacz M, Chmiel-Perzyńska I, et al. Zaburzenia psychiczne a nadczynność tarczycy. Curr Probl Psychiatry. 2011; 12(2): 146–151.
21. del Ghianda S, Tonacchera M, Vitti P. Thyroid and menopause. Climacteric. 2014; 17(3): 225–234, doi: 10.3109/13697137.2013.838554, indexed in Pubmed: 23998691.
22. Magierska J, Magierski R, Fendler W, et al. Clinical application of the Polish adaptation of the Montreal Cognitive Assessment (MoCA) test in screening for cognitive impairment. Neurol Neurochir Pol. 2012; 46(2): 130–139, indexed in Pubmed: 22581594.
23. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. Arch Clin Neuropsychol. 2006; 21(7): 623–643, doi: 10.1016/j.acn.2006.05.007, indexed in Pubmed: 17014981.

24. European Communities. Data Information on Women's Health in the European Union. Dresden 2009.
25. Alzheimer's Association. Alzheimer's disease facts and figures. 2012. www.alz.org/downloads/Facts_Figures_2012.pdf.
26. Carter CL, Resnick EM, Mallampalli M, et al. Sex and gender differences in Alzheimer's disease: recommendations for future research. J Womens Health (Larchmt). 2012; 21(10): 1018–1023, doi: 10.1089/jwh.2012.3789, indexed in Pubmed: 22917473.
27. Rapp SR, Legault C, Henderson VW, et al. Subtypes of mild cognitive impairment in older postmenopausal women: the Women's Health Initiative Memory Study. Alzheimer Dis Assoc Disord. 2010; 24(3): 248–255, doi: 10.1097/WAD.0b013e3181d715d5, indexed in Pubmed: 20473134.
28. Greendale GA, Huang MH, Wight RG, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. Neurology 2009; 72: 1850–1857.
29. Roberts LM, Pattison H, Roalfe A, et al. Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? Ann Intern Med. 2006; 145(8): 573–581, indexed in Pubmed: 17043339.
30. Beydoun MA, Beydoun HA, Kitner-Triolo MH, et al. Thyroid hormones are associated with cognitive function: moderation by sex, race, and depressive symptoms. J Clin Endocrinol Metab. 2013; 98(8): 3470–3481, doi: 10.1210/jc.2013-1813, indexed in Pubmed: 23690311.
31. Hogervorst E, Huppert F, Matthews FE, et al. Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. Psychoneuroendocrinology. 2008; 33(7): 1013–1022, doi: 10.1016/j.psyneuen.2008.05.008, indexed in Pubmed: 18640783.
32. Choi SM, Kim BC, Choi KH, et al. Thyroid status and cognitive function in euthyroid patients with early Parkinson's disease. Dement Geriatr Cogn Disord. 2014; 38(3–4): 178–185, doi: 10.1159/000359966, indexed in Pubmed: 24732425.
33. Gunnarsson T, Sjöberg S, Eriksson M, et al. Depressive symptoms in hypothyroid disorder with some observations on biochemical correlates. Neuropsychobiology. 2001; 43(2): 70–74, doi: 54869, indexed in Pubmed: 11174048.
34. van Boxtel MPJ, Menheere PP, Bekers O, et al. Thyroid function, depressed mood, and cognitive performance in older individuals: the Maastricht Aging Study. Psychoneuroendocrinology. 2004; 29(7): 891–898, doi: 10.1016/j.psyneuen.2003.08.002, indexed in Pubmed: 15177704.
35. Gan EH, Pearce SHS. Clinical review: The thyroid in mind: cognitive function and low thyrotropin in older people. J Clin Endocrinol Metab. 2012; 97(10): 3438–3449, doi: 10.1210/jc.2012-2284, indexed in Pubmed: 22865905.
36. Chachamovitz DS, Vigário PD, Silva SO, et al. Does low-normal serum TSH level adversely impact cognition in elderly adults and might methimazole therapy improve outcomes? Endocr J. 2016; 63(5): 495–505, doi: 10.1507/endocrj.EJ15-0458, indexed in Pubmed: 27052122.
37. Moon JH, Park YJ, Kim TH, et al. Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment in elderly: Korean Longitudinal Study on Health and Aging (KLoSHA). J Clin Endocrinol Metab. 2014; 99(2): 424–432, doi: 10.1210/jc.2013-3385, indexed in Pubmed: 24285689.
38. Wijsman LW, de Craen AJM, Trompet S, et al. Subclinical thyroid dysfunction and cognitive decline in old age. PLoS One. 2013; 8(3): e59199, doi: 10.1371/journal.pone.0059199, indexed in Pubmed: 23554996.
39. Ojala AK, Schalin-Jäntti C, Pitkälä KH, et al. Serum thyroid-stimulating hormone and cognition in older people. Age Ageing. 2016; 45(1): 155–157, doi: 10.1093/ageing/afv160, indexed in Pubmed: 26601696.
40. Laurberg P, Andersen S, Bülow Pedersen I, et al. Hypothyroidism in the elderly: pathophysiology, diagnosis and treatment. Drugs Aging. 2005; 22(1): 23–38, indexed in Pubmed: 15663347.
41. Resta F, Triggiani V, Barile G, et al. Subclinical hypothyroidism and cognitive dysfunction in the elderly. Endocr Metab Immune Disord Drug Targets. 2012; 12(3): 260–267, indexed in Pubmed: 22385117.
42. Ceresini G, Lauretani F, Maggio M, et al. Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti study. J Am Geriatr Soc. 2009; 57(1): 89–93, doi: 10.1111/j.1532-5415.2008.02080.x, indexed in Pubmed: 19054181.
43. Grigorova M, Sherwin BB. Thyroid hormones and cognitive functioning in healthy, euthyroid women: a correlational study. Horm Behav. 2012; 61(4): 617–622, doi: 10.1016/j.yhbeh.2012.02.014, indexed in Pubmed: 22373496.
44. Mizuma A, Goto Y, Takahashi W, et al. A Patient with Hashimoto's Encephalopathy Presenting with Convulsive Seizure Alone as the Initial Symptom. Clin Med Insights Case Rep. 2013; 6: 75–77, doi: 10.4137/CCRep.S10390, indexed in Pubmed: 23700379.
45. Nayak HK, Daga MK, Kumar R, et al. A series report of autoimmune hypothyroidism associated with Hashimoto's encephalopathy: an under diagnosed clinical entity with good prognosis. BMJ Case Rep. 2010; 2010, doi: 10.1136/bcr.01.2010.2630, indexed in Pubmed: 22797195.
46. Regal PJ. Antithyroid antibodies, cognition and instrumental activities of daily living in the elderly. Int J Geriatr Psychiatry. 2012; 27(12): 1317–1318, doi: 10.1002/gps.3767, indexed in Pubmed: 23132706.
47. Jabłkowska K., Karbownik-Lewińska M., Nowakowska K., Junik R., Lewiński A., Borkowska A. Pamięć operacyjna i funkcje wykonawcze w nadczynności tarczycy w przebiegu choroby Gravesa i Basedowa. Psychiatria Polska 2008; XLII; 2: 249–259.